ISSN 1936-8798/08/$34.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2008.02.003

Stent Malapposition After Sirolimus-Eluting and Bare-Metal Stent Implantation in Patients with ST-Segment Elevation Myocardial Infarction

Acute and 9-Month Intravascular Ultrasound Results of the MISSION! Intervention Study

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Objectives Acute and late stent malapposition (SM) after bare-metal stents (BMS) and sirolimus-eluting stents (SES) in ST-segment elevation myocardial infarction patients were studied.

Background Stent thrombosis may be caused by SM after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction patients.

Methods Post-procedure and follow-up intravascular ultrasound data were available in 184 out of 310 patients (60%; 104 SES, 80 BMS) included in the MISSION! Intervention Study. To determine the contribution of remodeling and changes in plaque burden to the change in lumen cross-sectional area (CSA) at SM sites, the change in lumen CSA (follow-up minus post-lumen CSA) was related to the change in external elastic membrane CSA (remodeling) and change in plaque and media CSA (plaque burden).

Results Acute SM was found in 38.5% SES patients and 33.8% BMS patients ($p = 0.51$), late SM in 37.5% SES patients and 12.5% BMS patients ($p < 0.001$). Acquired SM was found in 25.0% SES patients and 5.0% BMS patients ($p < 0.001$). Predictors of acute SM were reference diameter (SES: odds ratio [OR] 3.49, 95% confidence interval [CI] 1.29 to 9.43; BMS: OR 28.8, 95% CI 4.25 to 94.5) and balloon pressure (BMS: OR 0.74, 95% CI 0.58 to 0.94). Predictors of late SM were diabetes mellitus (SES: OR 0.16, 95% CI 0.02 to 1.35), reference diameter (BMS: OR 19.2, 95% CI 2.64 to 139.7), and maximum balloon pressure (BMS: OR 0.74, 95% CI 0.55 to 1.00). Change in lumen CSA was related to change in external elastic membrane CSA ($R = 0.73$, 95% CI 0.62 to 0.84) after SES implantation and to change in plaque and media CSA ($R = -0.62$, 95% CI −0.77 to −0.46) after BMS implantation. After SES implantation, acquired SM was caused by positive remodeling in 84% and plaque reduction in 16% of patients.

Conclusions Acute SM was common after SES and BMS stent implantation in ST-segment elevation myocardial infarction patients. After SES implantation, late acquired SM is common and generally caused by positive remodeling. (The MISSION! Intervention Study, ISRCTN62825862) (J Am Coll Cardiol Intv 2008;1:192–201) © 2008 by the American College of Cardiology Foundation

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Manuscript received December 10, 2007; revised manuscript received January 31, 2008, accepted February 7, 2008.

Although long-term angiographic results of drug-eluting stents (DES) are superior to the results obtained with bare-metal stents (BMS), the safety of DES became a major issue as DES are associated with an increased risk of late or very late stent thrombosis (1–3). It is difficult to determine the exact mechanism of stent thrombosis in individual patients. Renal failure, diabetes mellitus, stent implantation during acute myocardial infarction, insufficient antithrombotic therapy or premature discontinuation of dual antiplatelet therapy, implanted stent length, or bifurcation stenting have been identified as risk factors of stent thrombosis (1,2,4,5). From a pathological point of view, drug-induced delayed re-endothelialization of the endothelium seems to play an important role (6). Another factor associated with stent thrombosis is stent malapposition (SM) (7,8). Stent malapposition may be a sign of impaired healing or the result of suboptimal stent implantation. Stent malapposition may increase the thrombotic risk due to the presence of intraluminal stent struts. In patients with stable angina, several studies reported increased SM rates in DES-treated patients compared with BMS-treated patients (9,10). Limited data are reported about the incidence and mechanisms of SM after percutaneous coronary interventions in patients with ST-segment elevation myocardial infarction (STEMI) (11). This study reports on the incidence of acute and late SM within the Medical Image Sharing with Satellite Integrated Optical-Fiber Network Intervention Study, a randomized study comparing the efficacy of DES with BMS in STEMI patients, as studied by intravascular ultrasound imaging (IVUS).

Methods

Patient selection and randomization. The MISSION! Intervention Study was a single-center, single-blind, randomized controlled trial comparing sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Miami Lakes, Florida) and BMS (Vision, Guidant Corp., Indianapolis, Indiana) in STEMI patients. The study was approved by the Institutional Ethical Review Board. All patients gave informed consent before the procedure. An additional informed consent was obtained for follow-up angiography and IVUS imaging at 9 months. This study is a predefined substudy including patients in whom both post-procedural and 9-month IVUS results were available. The study design, inclusion and exclusion criteria, end point definition, and main outcomes of the study were published previously (12). Briefly, patients were eligible for participation if they had symptoms of acute myocardial infarction <9 h before arrival at the catheterization laboratory and the ECG revealed a STEMI. Key exclusion criteria included age <18 or >80 years; the presence of a left main lesion of ≥50% stenosis; triple vessel disease, defined as ≥50% stenosis in 3 major epicardial vessels; previous percutaneous coronary intervention or bypass grafting of the culprit vessel; failed thrombolytic therapy for the index infarction; reference diameter of the culprit lesion of <2.25 or >3.75 mm; and lesion length >24 mm. After successful positioning of the guidewire distal to the target lesion, patients were randomized to treatment with BMS or SES. The primary end point of the study was angiographic in-segment late loss at 9 months.

Study procedure and adjunct medication. Before the index procedure, all patients received 300 mg of aspirin, 300 to 600 mg of clopidogrel, and an intravenous bolus of abciximab (25 μg/kg), followed by a continuous infusion of 10 μg/kg/min for 12 h. At the beginning of the procedure, 5,000 IU of heparin were given. Lesions were treated according to current interventional practice. If more than 1 stent was required, additional assigned study stents were used. Stent size and length selection was based on visual estimation. Before and immediately after the intervention, 2 angiograms in orthogonal projections were obtained. The IVUS imaging was performed after stent implantation to document the angiographic result. Intravascular ultrasound-guided stent implantation was not performed to reflect routine angiography-guided stent implantation. Intravascular ultrasound imaging was performed with motorized pullback (0.5 mm/s) starting at least 10 mm distal to the stent and ending at the coronary ostium, using a 2.9-F 20-MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp., Rancho Cordova, California) (13). Each angiogram and ultrasound sequence was preceded by 200 to 300 μg of intracoronary nitroglycerin. After the procedure, aspirin (80 to 100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for 12 months. During follow-up, patients were treated with beta-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotension II-blockers, according to current guidelines (14). Patients were seen at the outpatient clinic at 30 days and 3, 6, and 12 months. Follow-up angiography and IVUS imaging was performed at 9 months.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
CSA = cross-sectional area
DES = drug-eluting stent(s)
EEM = external elastic membrane
IVUS = intravascular ultrasound
LBS = lumen behind stent
OR = odds ratio
P&M = plaque and media
SES = sirolimus-eluting stent(s)
SM = stent malapposition
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Quantitative coronary angiography. Coronary angiograms obtained at baseline, after completion of the stenting procedure, and at the 9-month follow-up were digitally recorded and analyzed blinded for the assigned treatment. Analyses were performed with automated edge-detection software (CMS version 6.0, Medis Medical Imaging Systems, Leiden, the Netherlands) at the worst view projection

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 2, 2008
APRIL 2008:192–201

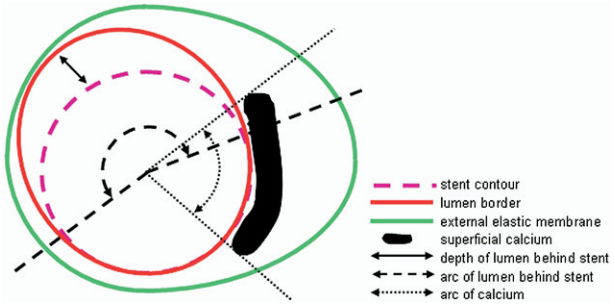

Figure 1. IVUS Contours and Measurements

Schematic diagram illustrating intravascular ultrasound (IVUS) contours and measurements.

(15). The stented zone and the proximal and distal 5-mm stent edges were evaluated. The reference diameter was determined by interpolation. Within the stented segment, minimum luminal diameter and percentage diameter stenosis were determined. The percentage diameter stenosis was defined as the difference between reference and actual diameter divided by the reference diameter and multiplied by 100. Late loss was defined as the difference between the post-procedural and follow-up minimum luminal diameter.

IVUS analysis. IVUS images were analyzed offline, using quantitative IVUS analysis software (QCU-CMS 4.14, Medis, Leiden, the Netherlands) (16). Analyses were performed by 2 experienced analysts blinded for the assigned treatment. A SM was defined as a separation of at least 1 stent strut from the intimal surface that was not overlapping a side branch and had IVUS evidence of blood speckles behind the strut (17). A SM was defined as *acute* if present immediately after the index procedure, as *late* if present at the 9-month follow-up, as *resolved* if present after stent implantation but not at follow-up, as *persistent* if present both after stent implantation and at follow-up, and as *acquired* if present at follow-up but not after stent implantation. The identification of SM sites in post-procedural images was performed independently from follow-up images. Hereafter, the post-procedural IVUS images were compared side by side with the follow-up images to determine whether the SM resolved, persisted, or was acquired. Corresponding post-procedural and follow-up images at the site of maximum lumen area behind the stent were selected. The external elastic membrane (EEM) cross-sectional area (CSA), stent CSA, lumen CSA inside the stent, and lumen CSA (inside and outside the stent) were determined in selected frames (Fig. 1). Furthermore, the maximum arc of SM, the maximum depth of the lumen behind the stent (LBS) and the maximum calcium arc at the site of SM were determined. The LBS CSA was calculated by subtracting the lumen CSA inside the stent from the lumen CSA. The neointimal CSA was calculated by subtracting the lumen CSA inside the stent from the stent CSA. Plaque burden was defined as the plaque plus media (P&M) CSA and was calculated by subtracting the lumen CSA from the EEM CSA. Percentage plaque burden was calculated by dividing the P&M CSA by the EEM CSA and multiplying by 100%. Vessel remodeling was calculated by follow-up minus post-procedure EEM CSA (ΔEEM CSA). Positive remodeling was defined as an increase in EEM CSA and negative remodeling as a decrease in EEM CSA. Change (Δ) in plaque burden was calculated by follow-up minus post-procedure P&M CSA (ΔP&M CSA). Plaque increase was defined as an increase and plaque reduction as a decrease of the P&M CSA.

Statistical analysis. Statistical analysis was conducted with SPSS 12.0.1 statistical analysis software (SPSS Inc., Chicago, Illinois). Categorical variables are presented as number (%) and continuous variables as mean ± standard deviation. Analysis of post-procedural and follow-up angiographic and IVUS data was conducted according to the number of patients for which complete data were available. Continuous variables were compared between the treatment groups with a *t* test or, in case of non-normality, with an equivalent nonparametric test. Categorical variables were compared with chi-square test or Fisher exact test. The correlation between variables was calculated using the Pearson product moment correlation method. Multivariate logistic regres-

Table 1. Baseline Clinical and Angiographic Characteristics

Characteristic	SES (n = 104)	BMS (n = 80)	p Value
Age (yrs)	58.6 ± 11.5	58.9 ± 11.8	0.84
Male gender (%)	76 (73.1)	65 (81.3)	0.19
Diabetes mellitus (%)	10 (9.6)	3 (3.8)	0.12
Current smoker (%)	62 (59.6)	41 (51.3)	0.28
Hypercholesterolemia (%)	22 (21.2)	11 (13.8)	0.19
Hypertension (%)	36 (34.6)	22 (27.5)	0.30
Family history of CAD (%)	45 (43.3)	26 (32.5)	0.14
Prior myocardial infarction (%)	5 (4.8)	3 (3.8)	1.00
Prior PCI or CABG (%)	2 (1.9)	1 (1.3)	1.00
Target vessel (%)			
LAD	60 (57.7)	48 (60.0)	0.15
RCA	25 (24.0)	25 (31.3)	
LCX	19 (18.3)	7 (8.7)	
Multivessel disease (%)	37 (35.6)	28 (35.0)	0.94
TIMI flow grade (%)			
0–1	73 (70.2)	56 (70.0)	0.98
2–3	31 (29.8)	24 (30.0)	
Vessel reference diameter (mm)	2.81 ± 0.56	2.93 ± 0.55	0.16
Minimal luminal diameter (mm)	0.23 ± 0.36	0.23 ± 0.38	0.96
Diameter stenosis (%)	92.0 ± 12.4	92.6 ± 12.0	0.74

BMS = bare-metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; LAD = left anterior descending; LCX = left circumflex (artery); PCI = percutaneous coronary intervention; RCA = right coronary artery; SES = sirolimus-eluting stent; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Clinical, Angiographic, and Procedural Correlates of SM After SES Implantation (n= 104)

	Acute (Post-Procedure)		Late (Follow-Up)		
	SM	No SM	SM	No SM	Acquired SM*
No. of patients (%)	40 (38.5)	64 (61.5)	39 (37.5)	65 (62.5)	26 (25.0)
Clinical characteristics					
Male gender (%)	31 (77.5)	45 (70.3)	29 (74.4)	47 (72.3)	21 (80.8)
Age (yrs)	58.7 ± 11.3	58.5 ± 11.7	59.6 ± 10.2	57.9 ± 12.3	60.1 ± 9.2
Diabetes mellitus (%)	4 (10.0)	6 (9.4)	1 (2.6)	9 (13.8)	0 (0.0)†
Angiographic characteristics					
Target vessel (%)					
LAD	28 (70.0)	32 (50.0)	22 (56.4)	38 (58.5)	11 (42.3)
RCA	7 (17.5)	18 (28.1)	9 (23.1)	16 (24.6)	7 (26.9)
LCX	5 (12.5)	14 (21.9)	8 (20.5)	11 (16.9)	8 (30.8)
Multivessel disease (%)	11 (27.5)	26 (40.6)	16 (41.0)	21 (32.3)	11 (42.3)
TIMI flow grade 0 or 1 at baseline (%)	24 (60.0)	49 (76.6)	28 (71.8)	45 (69.2)	19 (73.1)
Vessel reference diameter					
Post-procedure (mm)	3.16 ± 0.41	2.90 ± 0.48†	3.05 ± 0.45	2.97 ± 0.48	3.11 ± 0.50
Minimal luminal diameter (mm)					
Baseline	0.26 ± 0.35	0.21 ± 0.37	0.22 ± 0.34	0.24 ± 0.38	0.24 ± 0.39
Post-procedure	2.81 ± 0.37	2.59 ± 0.40†	2.74 ± 0.39	2.64 ± 0.41	2.83 ± 0.39
Diameter stenosis post-procedure (%)	10.8 ± 5.8	10.2 ± 7.6	9.7 ± 7.1	10.9 ± 6.8	8.5 ± 6.9
Late luminal loss at follow-up (mm)					
Proximal edge	0.11 ± 0.35	0.22 ± 0.29	0.15 ± 0.34	0.19 ± 0.31	0.24 ± 0.35
In-stent	0.09 ± 0.25	0.18 ± 0.27	0.13 ± 0.26	0.15 ± 0.27	0.15 ± 0.31
Distal edge	−0.04±0.34	0.03 ± 0.31	−0.07 ± 0.33	0.05 ± 0.31	−0.08 ± 0.35
Procedural characteristics					
Direct stenting (%)	18 (45.0)	24 (37.5)	16 (41.0)	26 (40.0)	11 (42.3)
No. of stents implanted	1.30 ± 0.56	1.28 ± 0.52	1.33 ± 0.62	1.26 ± 0.48	1.31 ± 0.62
Implanted stent length (mm)	24.8 ± 11.7	26.0 ± 11.3	27.2 ± 12.2	24.5 ± 10.9	26.8 ± 10.8
Post-dilatation (%)	17 (42.5)	23 (35.9)	15 (38.5)	25 (38.5)	11 (42.3)
Maximum balloon diameter (mm)	3.49 ± 0.27	3.34 ± 0.29†	3.42 ± 0.24	3.38 ± 0.31	3.42 ± 0.23
Maximal balloon pressure (atm)	12.8 ± 2.4	12.4 ± 2.2	12.8 ± 2.1	12.4 ± 2.3	13.2 ± 2.1
Maximal balloon to artery ratio	1.18 ± 0.17	1.18 ± 0.19	1.16 ± 0.17	1.19 ± 0.18	1.14 ± 0.19

*Comparison of acquired versus no SM at follow-up. †$p < 0.05$
SM = stent malapposition; other abbreviations as in Table 1.

sion analysis was performed to determine independent clinical, angiographic, and procedural predictors of acute, late, and acquired SM by entering all univariate predictors ($p < 0.10$) in the model. The variables analyzed in the model were assigned stent type, gender, diabetes mellitus, baseline Thrombolysis In Myocardial Infarction (TIMI) flow, pre-dilation, implanted stent length, maximal balloon pressure, balloon-to-artery ratio, vessel reference diameter, post-procedural percentage diameter stenosis, and the interaction of these variables with the assigned stent type. All p values were 2-sided, and a p value <0.05 was considered statistically significant.

Results

Patients. Patient and angiographic characteristics are summarized in Table 1. Of 310 patients included in the MISSION! Intervention Study, follow-up angiography was performed in 254 patients (84%). Post-procedural and follow-up IVUS image loops qualified for quantitative analysis of the stent, lumen, and SM evaluation in 184 patients (60%). Clinical, angiographic, and procedural correlates of acute and late SM in these patients are listed in Table 2 for SES and Table 3 for BMS. Within these 184 patients, 129 SM sites were identified and analyzed (Table 4). Three sites were not analyzable because of severe calcification.

Acute SM. Acute SM was found in 40 out of 104 (49 sites) SES patients (38.5%) and in 27 out of 80 (32 sites) BMS patients (33.8%) ($p = 0.51$). Univariate predictors of acute SM after SES implantation were vessel reference diameter (odds ratio [OR] 3.68, 95% confidence interval [CI] 1.38 to 9.81; $p = 0.009$) and baseline TIMI flow grade 2 or 3 (OR 2.18, 95% CI 0.92 to 5.13; $p = 0.08$). After BMS

Table 3. Clinical, Angiographic, and Procedural Correlates of SM After BMS Implantation (n = 80)

	Acute (Post-Procedure)		Late (Follow-Up)		
	SM	No SM	SM	No SM	Acquired SM*
No. of patients (%)	27 (33.8)	53 (66.2)	10 (12.5)	70 (87.5)	4 (5.0)
Clinical characteristics					
Male gender (%)	21 (77.8)	44 (83.0)	9 (90.0)	56 (80.0)	4 (100.0)
Age (yrs)	61.4 ± 12.4	57.7 ± 11.4	63.3 ± 11.0	58.3 ± 11.9	66.0
Diabetes mellitus (%)	1 (3.7)	2 (3.8)	0 (0.0)	3 (4.3)	0 (0.0)
Angiographic characteristics					
Target vessel (%)					
LAD	15 (55.6)	33 (62.3)	5 (50.0)	43 (61.4)	1 (25.0)
RCA	9 (33.3)	16 (30.2)	4 (40.0)	21 (30.0)	3 (75.0)
LCX	3 (11.1)	4 (7.5)	1 (10.0)	6 (8.6)	0 (0.0)
Multivessel disease (%)	10 (37.0)	18 (34.0)	4 (40.0)	24 (34.3)	1 (25.0)
TIMI flow grade 0 or 1 at baseline (%)	17 (63.0)	39 (73.6)	5 (50.0)	51 (72.9)	1 (25.0)
Vessel reference diameter					
Post-procedure (mm)	3.39 ± 0.37	2.95 ± 0.39†	3.48 ± 0.39	3.04 ± 0.42†	3.43
Minimal luminal diameter (mm)					
Baseline	0.33 ± 0.51	0.17 ± 0.28	0.52 ± 0.66	0.18 ± 0.31	0.98
Post-procedure	2.94 ± 0.31	2.62 ± 0.33†	2.94 ± 0.26	2.70 ± 0.36†	3.04
Diameter stenosis post-procedure (%)	13.2 ± 7.4	10.7 ± 8.1	15.2 ± 7.2	11.0 ± 7.9	11.0
Late luminal loss at follow-up (mm)					
Proximal edge	0.40 ± 0.60	0.28 ± 0.41	0.28 ± 0.35	0.33 ± 0.51	0.20
In-stent	1.01 ± 0.51	0.81 ± 0.39	0.84 ± 0.41	0.89 ± 0.45	0.69
Distal edge	0.10 ± 0.48	0.16 ± 0.45	−0.08 ± 0.33	0.17 ± 0.46	−0.06
Procedural characteristics					
Direct stenting (%)	9 (33.3)	24 (45.3)	4 (40.0)	29 (41.4)	3 (75.0)
No. of stents implanted	1.41 ± 0.50	1.32 ± 0.58	1.40 ± 0.52	1.34 ± 0.56	1.00
Implanted stent length (mm)	27.7 ± 10.2	26.0 ± 10.7	28.5 ± 10.7	26.3 ± 10.5	23.0
Post-dilatation (%)	11 (40.7)	13 (24.5)	3 (30.0)	21 (30.0)	0 (0.0)
Maximum balloon diameter (mm)	3.54 ± 0.24	3.39 ± 0.29†	3.55 ± 0.16	3.42 ± 0.29	3.50
Maximal balloon pressure (atm)	11.6 ± 2.8	12.6 ± 2.3	11.0 ± 2.6	12.4 ± 2.4	11.0
Maximal balloon to artery ratio	1.09 ± 0.21	1.19 ± 0.15	1.09 ± 0.24	1.16 ± 0.17	1.03

*Only the mean value is presented because of low numbers. No statistical comparison was performed. †$p < 0.05$.
Abbreviations as in Tables 1 and 2.

implantation, univariate predictors of acute SM were vessel reference diameter (OR 20.1, 95% CI 4.39 to 92.4; $p < 0.001$), maximum balloon pressure (OR 0.84, 95% CI 0.69 to 1.02; $p = 0.08$), and balloon-to-artery ratio (OR 0.03, 95% CI 0.00 to 0.71; $p = 0.03$). Multivariate predictors of acute SM were vessel reference diameter (OR 3.49, 95% CI 1.29 to 9.43; $p = 0.01$) after SES implantation and vessel reference diameter (OR 28.8, 95% CI 4.25 to 94.5; $p < 0.001$) and maximum balloon pressure (OR 0.74, 95% CI 0.58 to 0.94; $p = 0.01$) after BMS implantation.

Stent malapposition persisted in 19 out of 40 (28 sites) SES patients (48%) compared with 9 out of 27 (11 sites) BMS patients (33%) ($p = 0.15$). In the remaining acute SM patients, SM resolved (although in 3 SES patients acute SM resolved, but late SM developed at another site). Compared with resolved SES SM sites, persistent SES SM sites had larger LBS CSA (2.7 vs. 1.6 mm^2, $p = 0.005$), larger depth of the LBS (0.69 vs. 0.48 mm, $p = 0.02$), and larger arc of the LBS (166° vs. 135°, $p = 0.04$) and were located at sites with more plaque burden (49% vs. 44%, $p = 0.04$). Persistent BMS SM sites had a larger depth of the LBS (0.71 vs. 0.51 mm, $p = 0.02$) and were located at sites with larger EEM CSA (24.0 vs. 19.6 mm^2, $p = 0.01$) and P&M CSA (12.0 vs. 8.8 mm^2, $p = 0.007$) than the resolved BMS SM sites. Moreover, these sites demonstrated less negative remodeling (ΔEEM CSA: 0.7 vs. −1.1 mm^2, $p < 0.001$) and less increase in P&M CSA (ΔP&M CSA: 1.1 vs. 3.0 mm^2, $p = 0.003$).

Late SM. At the 9-month follow-up, late SM was observed in 39 of 104 (73 sites) SES patients (37.5%) and in 10 of 80 (14 sites) BMS patients (12.5%, $p < 0.001$). Besides persistent SM, acquired SM at 9 months was common after SES implantation but rare after BMS implantation (26 of 104 vs. 4 of 80 patients, 25.0% vs.

Table 4. IVUS Characteristics of Resolved, Persistent, and Acquired SM Sites After SES and BMS Implantation

	Resolved			Persistent			Acquired		p Value†	
Characteristics	SES	BMS	p Value	SES	BMS	p Value	SES	BMS*	SES R vs. P	BMS R vs. P
No. of SM sites	21	21		28	11		45	3		
LBS CSA (mm^2)			0.32							
Post-procedure	1.6 ± 0.7	1.9 ± 1.3		2.7 ± 1.7	3.2 ± 2.5	0.55			0.005	0.14
Follow-up				2.5 ± 1.8	4.1 ± 3.0	0.13	3.2 ± 1.7	4.1		
LBS length (mm)			0.68							
Post-procedure	1.4 ± 1.0	1.6 ± 1.6		1.5 ± 1.4	2.0 ± 1.8	0.34			0.75	0.47
Follow-up				1.3 ± 1.3	1.7 ± 1.6	0.44	2.7 ± 2.3	1.2		
LBS maximum depth (mm)			0.59							
Post-procedure	0.48 ± 0.16	0.51 ± 0.21		0.69 ± 0.36	0.71 ± 0.23	0.86			0.02	0.02
Follow-up				0.69 ± 0.34	0.77 ± 0.31	0.49	0.69 ± 0.30	0.84		
LBS arc (°)			0.33						0.04	
Post-procedure	135 ± 37	150 ± 60		166 ± 64	188 ± 91	0.40				0.23
Follow-up				171 ± 53	176 ± 119	0.89	205 ± 71	226		
Calcium (%)	4 (19)	4 (19)	1.00	9 (32)	5 (46)	0.79	24 (53)	1 (33)	0.41	0.12
Stent CSA (mm^2)	8.9 ± 1.4	8.8 ± 1.5	0.83	8.1 ± 1.7	8.9 ± 1.0	0.07	8.2 ± 1.5	9.1	0.09	0.82
Plaque burden (%)	44 ± 8	44 ± 7	0.90	49 ± 7	50 ± 10	0.64	55 ± 9	64	0.04	0.07
Lumen CSA (mm^2)										
Post-procedure	10.5 ± 1.7	10.8 ± 2.4	0.65	10.8 ± 2.9	12.0 ± 3.1	0.27	8.2 ± 1.5	9.1	0.58	0.22
Follow-up	8.6 ± 1.5	6.6 ± 1.6	<0.001	10.7 ± 3.0	11.6 ± 3.9	0.47	11.4 ± 2.2	12.9	0.003	0.002
ΔLumen CSA (mm^2)	−1.9 ± 0.7	−4.1 ± 1.9	<0.001	−0.2 ± 1.4	−0.4 ± 1.5	0.65	3.2 ± 1.7	3.9	<0.001	<0.001
EEM CSA (mm^2)										
Post-procedure	19.1 ± 4.3	19.6 ± 4.6	0.71	21.3 ± 6.3	24.0 ± 4.4	0.20	19.0 ± 5.6	25.7	0.17	0.01
Follow-up	18.3 ± 3.9	18.5 ± 4.0	0.86	21.1 ± 6.1	24.7 ± 4.6	0.08	21.8 ± 5.3	27.1	0.07	<0.001
ΔEEM CSA	−0.8 ± 1.5	−1.1 ± 1.2	0.49	−0.2 ± 1.1	0.7 ± 1.5	0.04	2.8 ± 2.0	1.4	0.12	0.001
P&M CSA (mm^2)										
Post-procedure	8.6 ± 3.3	8.8 ± 2.8	0.82	10.5 ± 4.2	12.0 ± 3.4	0.29	10.8 ± 4.8	16.5	0.10	0.007
Follow-up	9.6 ± 3.0	11.8 ± 3.3	0.03	10.4 ± 3.5	13.1 ± 2.8	0.03	10.4 ± 4.0	14.1	0.41	0.29
ΔP&M CSA	1.0 ± 1.6	3.0 ± 1.5	<0.001	−0.1 ± 1.3	1.1 ± 1.8	0.04	−0.4 ± 1.5	−2.4	0.01	0.003
Neointima CSA (mm^2)	0.2 ± 0.3	2.0 ± 1.2	<0.001	0.1 ± 0.2	0.7 ± 0.9	0.04	0.0 ± 1.1	0.2	0.28	0.004

*Only the mean is presented because of low numbers; no statistical comparison was performed. †Comparison between resolved (R) and persistent (P) SM sites.
CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; LBS = lumen behind stent; P&M = plaque and media; other abbreviations as in Tables 1 and 2.

5.0%; $p < 0.001$). The only predictor of acquired SM was assigned SES stent (OR 9.43, 95% CI 2.73 to 32.6; $p < 0.001$). Diabetes mellitus was associated with a lower rate of late SM after SES implantation (OR 0.16, 95% CI 0.02 to 1.35; $p = 0.09$). Univariate predictors of late SM after BMS implantation were vessel reference diameter (OR 15.3, 95% CI 2.20 to 106.1; $p = 0.006$) and maximum balloon pressure (OR 0.79, 95% CI 0.60 to 1.04; $p = 0.10$). Multivariate predictors of late SM after BMS implantation were vessel reference diameter (OR 19.2, 95% CI 2.64 to 139.7; $p = 0.004$) and maximum balloon pressure (OR 0.74, 95% CI 0.55 to 1.00; $p = 0.05$). There was no relation between the presence and arc of calcium and the persistence of acute SM or the development of acquired SM.

Mechanism of lumen CSA change. The ΔEEM CSA (positive or negative remodeling) and ΔP&M CSA (plaque increase or reduction) during the follow-up period for each SM site are plotted in Figure 2. After BMS implantation, Δlumen CSA was mainly associated with ΔP&M CSA ($R = -0.62$, 95% CI −0.77 to −0.46; $p < 0.001$) and less with ΔEEM CSA ($R = 0.38$, 95% CI 0.23 to 0.54; $p < 0.001$) (Fig. 3A). The Δlumen CSA after SES implantation was strongly associated with ΔEEM CSA ($R = 0.73$, 95% CI 0.62 to 0.84; $p < 0.001$) and weakly associated with ΔP&M CSA ($R = -0.27$, 95% CI −0.38 to −0.16; $p < 0.001$) (Fig. 3B). Examples of the relation between Δlumen CSA with ΔEEM CSA and ΔP&M CSA are given in Figure 4. The dominant mechanism of development of acquired SM after SES implantation (45 sites) was positive remodeling in 38 sites (84%) and plaque reduction in 7 sites (16%). Compared to sites with positive remodeling, plaque reduction sites were located at sites with larger stent CSA (9.7 vs. 8.0 mm^2), larger EEM CSA (26.4 vs. 17.6 mm^2,

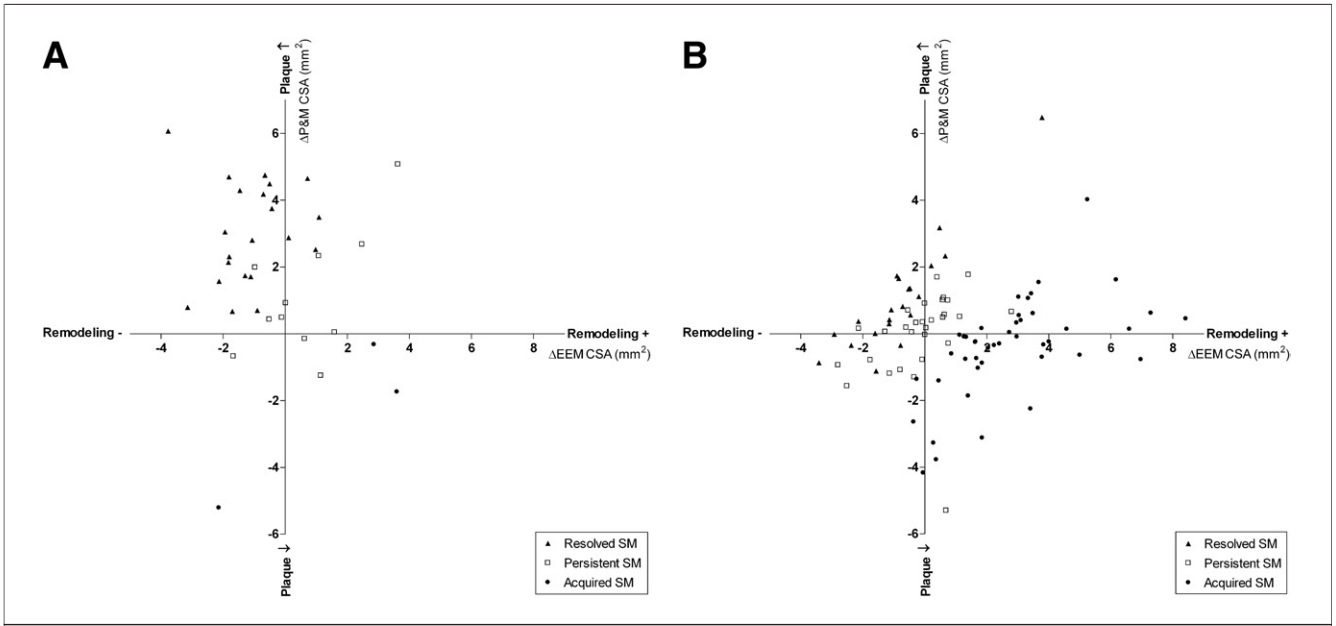

Figure 2. Change of EEM and P&M CSA During the Follow-Up Period for All Individual SM Sites

(A) Bare-metal stent (BMS); **(B)** sirolimus-eluting stent (SES). The stent malapposition (SM) sites are categorized as resolved, persistent, or acquired SM. Delta (Δ) denotes change (follow-up minus post-procedure). **(A)** BMS: Most of the acute SM sites (resolved and persistent) are located above the x axis, indicating an increase in the plaque and media (P&M) cross-sectional area (CSA) during the follow-up period. Acquired SM sites are very rare after BMS implantation. **(B)** SES: The external elastic membrane (EEM) and P&M CSA are virtually unchanged in most persistent SM sites. Acquired SM sites are mostly located around the positive x axis, indicating that positive remodeling (enlargement of the EEM CSA, while the P&M CSA remains virtually unchanged) is the mechanism of development of SM in these sites. In a minority of sites, plaque reduction (decrease of the P&M CSA, while the EEM CSA remains virtually unchanged) plays a role.

p = 0.02), larger P&M CSA (16.8 vs. 9.7 mm^2, p = 0.04) and larger plaque burden (61% vs. 54%, p = 0.04) containing less calcium (14% vs. 61%, p = 0.04). No differences were found between acquired SM sites within the BMS group because of limited numbers and lack of statistical power.

Clinical outcome. During 12 months of follow-up, none of the patients included in this analysis died. Myocardial infarction occurred in 3 SES patients and 4 BMS patients, all related to revascularization procedures (p = 0.47). These myocardial infarctions were only minimal troponin T leaks. Target vessel revascularization was performed in 8 BMS patients and 1 SES patient (p = 0.004). Target lesion revascularization was performed in 6 BMS and 0 SES patients (p = 0.005). None of the patients included in this study experienced stent thrombosis.

Discussion

Key findings of this study were: 1) acute SM was frequently observed in SES- and BMS-treated STEMI patients; 2) late SM was common after SES implantation, but was also observed after BMS implantation; 3) acquired SM occurred almost exclusively after SES implantation; 4) the dominant mechanism of lumen change at SM sites during follow-up was related to vessel remodeling in SES patients and to changes in plaque burden in BMS patients; and 5) acquired SM after SES implantation was caused by positive remodeling in the majority of cases (84%) and plaque reduction in a limited number of cases (16%).

Predictors of acute SM. Acute SM occurs at a similar rate after SES (38.5%) and BMS (33.8%) implantation in STEMI patients. In patients with stable angina, post-procedural SM rates of 11.5% after paclitaxel-eluting stent (10) and 17.9% to 25% after SES implantation (18,19) and 12.5% after zotarolimus-eluting stent implantation were reported (20). Although the angiographic results of our study were comparable to these studies, the higher rate of acute SM may be related to the presence of thrombus in STEMI patients, to differences in lesion characteristics (e.g., stable vs. unstable lesions), or dynamic changes in vessel dimension after restoration of flow and stent implantation. Independent predictors of acute SM were a larger vessel reference diameter and a lower maximum balloon pressure suggesting that stents in larger vessels were more often underexpanded and that acute SM in this study partly could have been avoided by using larger balloons and higher pressures (21). Stent underexpansion is common after angiography-guided stent implantation as has been demonstrated in several studies applying IVUS-guided implantation techniques (13,22). However, a correlation of SM with vessel diameters has, as far as we know, not been reported before. As stent underexpansion has been related to stent

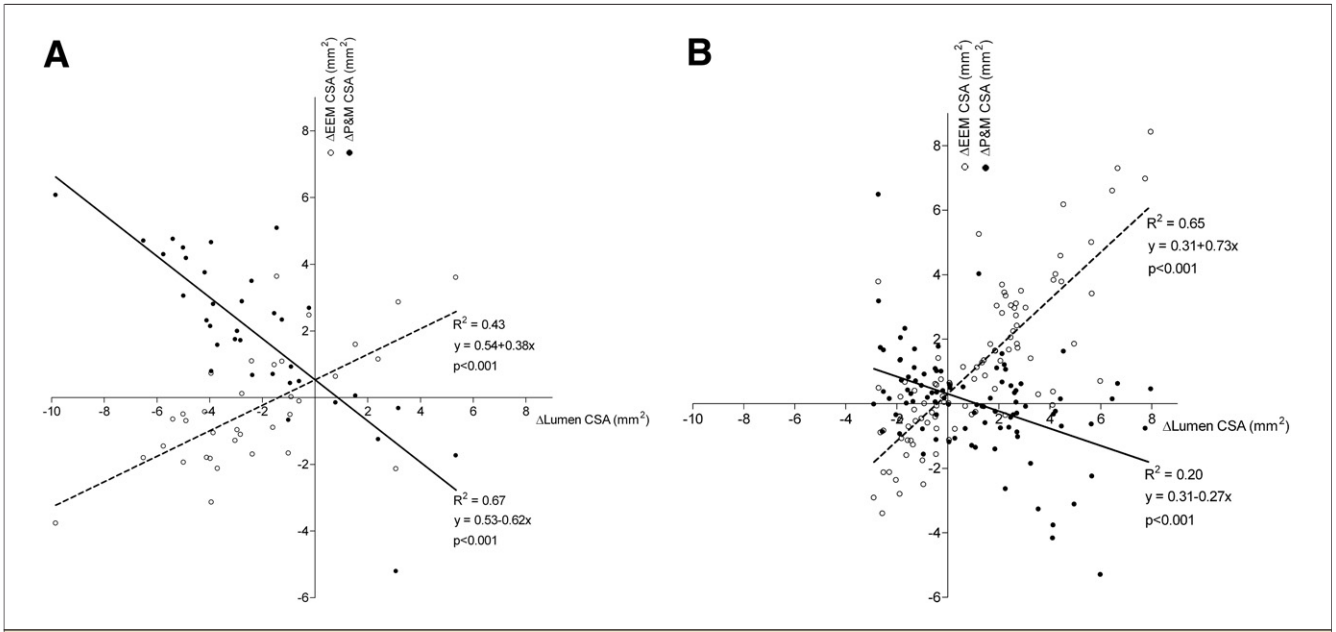

Figure 3. Mechanism of Change in Lumen CSA During the Follow-Up Period

(A) BMS; **(B)** SES. Delta (Δ) denotes change (follow-up minus post-procedure). **(A)** BMS: Changes of the lumen CSA are predominantly determined by changes in P&M CSA, which is positive in the majority of sites. Most likely this is due to neointimal growth. Clearly, remodeling (mostly negative) plays a small role in change of the lumen CSA. **(B)** SES: Change of the lumen CSA is mainly caused by remodeling after SES implantation, either negative (below x axis) or positive (above x axis). The P&M CSA remains virtually unchanged in most SM sites. Some SM sites demonstrate a clear reduction in P&M CSA, which may be due at least in part to resolution of thrombus behind the stent. Abbreviations as in Figure 2.

thrombosis and restenosis, efforts should be directed to obtain optimal expansion (23,24).

Predictors of late and acquired SM. Late SM was observed in 37.5% of the patients after SES implantation and 12.5% after BMS implantation. These figures are comparable with findings of other studies reporting a 31.8% late SM rate after SES implantation (11) and 11.5% after BMS implantation (25). In both studies, stent implantation in STEMI patients was an independent predictor of late SM, which underlines the potential risk of SM in this group of patients. The only factor related to a lower late SM rate after SES implantation was diabetes mellitus, a known subgroup of patients demonstrating more neointimal growth as compared with nondiabetic patients. Poor glycemic control has been associated with diminished efficacy of sirolimus on smooth muscle cell proliferation, which may explain the absence of late SM (26). After BMS implantation, larger vessel diameter and lower maximum balloon pressure were independent predictors of late SM. Late SM after BMS implantation seems therefore avoidable in the majority of lesions by more-aggressive implantation techniques, as discussed earlier. As diabetes mellitus in BMS patients was associated with a significant restenosis rate, the role of diabetes in late SM could not be studied. Although avoidance of stent underexpansion may lower the risk of late SM after SES implantation by reducing the rate of persistent SM, it is unknown whether a more aggressive implantation technique will lower or increase the rate of acquired SM in SES patients.

Mechanisms of SM. As demonstrated with IVUS, the dominant mechanism of lumen change at SM sites during the follow-up period was vessel remodeling after SES implantation and changes in plaque burden after BMS implantation (although vessel remodeling occurred also after BMS implantation) (27,28). Of interest in SES patients, vessel remodeling was found at SM sites with lumen increase and SM sites with lumen decrease. These findings emphasize that the main effect of SES is inhibition of neointimal growth. Moreover, it suggests that there is a patient- or lesion site-dependent sensitivity for vessel remodeling, resulting in disappearance, persistence, or appearance of SM. In this study, the only patient-dependent protective factor was diabetes mellitus as discussed earlier, which was also reported by others (10). A patient-dependent factor that has been associated with acquired SM due to positive remodeling is a hypersensitivity reaction to the polymer coating of SES (29). Induction of apoptosis by sirolimus may also play a role in remodeling after SES implantation, especially at sites of severe vessel damage during implantation (30,31).

Compared with acute SM sites associated with SES implantation, persistent SM sites were associated with larger LBS CSA, arc, and length. After BMS implantation, the LBS was only deeper compared with the LBS at resolved SM sites. These findings indicate that after SES or

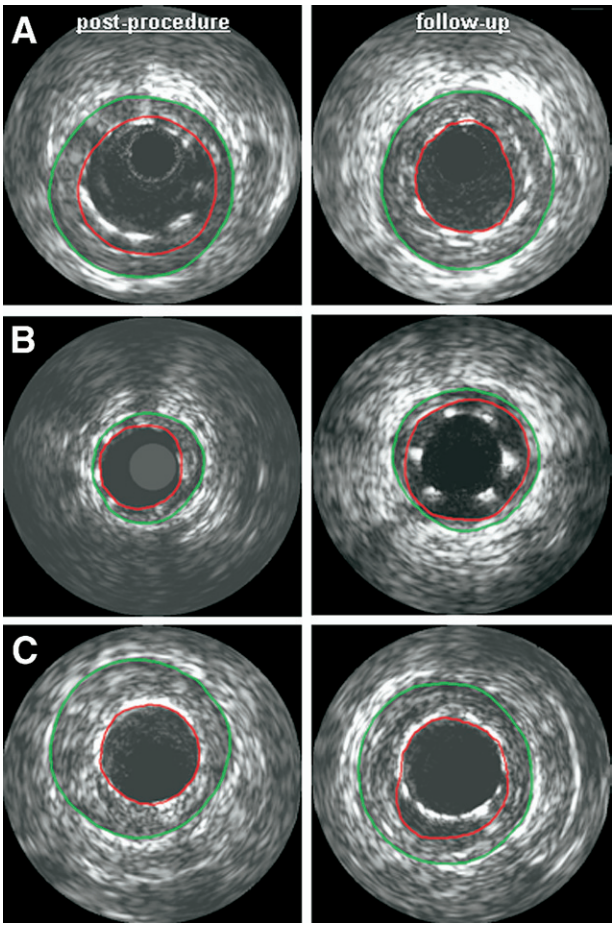

Figure 4. Examples of the Mechanism of Resolved and Acquired SM

The **green circle** indicates the EEM and the **red circle** the lumen contour. Delta (Δ) denotes change (follow-up minus post-procedure). **(A)** Resolved proximal edge SM due to increase of plaque burden and some negative remodeling. (Stent CSA: 10.7 mm^2, lumen behind stent [LBS] CSA: 5.7 mm^2, ΔEEM CSA: −2.1 mm^2, ΔP&M CSA: 4.9 mm^2, Δlumen CSA: −7.0 mm^2). **(B)** Acquired body SM because of positive remodeling. (Stent CSA: 6.1 mm^2, LBS CSA: 7.0 mm^2, ΔEEM CSA: 7.1 mm^2, ΔP&M CSA: 0.1 mm^2, Δlumen CSA: 7.0 mm^2). **(C)** Acquired body SM because of plaque reduction. (Stent CSA: 8.6 mm^2, LBS CSA: 3.3 mm^2, ΔEEM CSA: 0.2 mm^2, ΔP&M CSA: 3.2 mm^2, Δlumen CSA: 3.3 mm^2). Abbreviations as in Figure 2.

BMS implantation, disappearance of acute SM cannot be expected if the SM site is too large or too deep. After SES implantation, 55% of the acute SM sites persisted. In line with these observations, Hong et al. (11) even reported a 100% persistence rate of acute SM after SES implantation.

As suggested by others (11), a minority of lesions (16%) actually showed plaque reduction as a mechanism of acquired SM after SES implantation. Most likely, plaque reduction is due to thrombus resolution, because these sites could be characterized by huge amounts of plaque burden with noncalcified plaque. Because it is virtually impossible to discriminate between atherosclerotic plaque and thrombus using IVUS (especially behind stent struts), definite conclusions about the mechanism of development of SM in sites demonstrating a reduction in plaque burden cannot be drawn. Plaque reduction may also be the result of reduction in atherosclerotic plaque due to medication started after the myocardial infarction (e.g., statin therapy).

Clinical outcome. Although both acute and late SM were frequently observed, stent thrombosis did not occur. However, aspirin was prescribed indefinitely and clopidogrel was prescribed for 12 months. Because late SES stent thrombosis is mainly associated with discontinuation of antiplatelet therapy, events may be expected beyond 12 months (1,2,4).

Study limitations. The MISSION! Intervention Study was primarily an angiographic study focusing on angiographic end points. Nevertheless, this large study also intended to evaluate the mechanisms of acute and late SM by IVUS in STEMI patients, making the analyses reasonable and reliable. Moreover, baseline characteristics between SES and BMS patients were comparable, allowing a reliable comparison between both types of stents.

Conclusions

Acute SM is frequently observed after both SES and BMS implantation in STEMI patients. Late SM is rare after BMS and seems to be related to stent underexpansion in most patients. After SES implantation, late SM is common due to either persistence of acute SM or development of acquired SM. Positive vessel remodeling is the cause of acquired SM in most SES patients; however, in a minority of lesions plaque reduction causes late SM.

Acknowledgments

The authors acknowledge the following members of the Clinical Events Committee: Dr. A. V. G. Bruschke, Leiden, the Netherlands, and Dr. S. A. I. P. Trines, Leiden University Medical Center, Leiden, the Netherlands.

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